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Breast Conserving Surgery and Intraoperative Electron Radiotherapy (IOERT) Among Cases of Ductal Carcinoma In Situ

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ABSTRACT

Background: Ductal Carcinoma In Situ (DCIS) which has recently been renamed into Ductal Intraepithelial Neoplasia (DIN), is a malignant cell proliferation without invasion to basement membrane of ducts or lobules of breast. DCIS consists 20-30% of newly diagnosed breast cancers in some Western countries due to higher diagnosis resulting from screening by mammography. Relative Risk (RR) of invasive ductal carcinoma is 8-10 times in DCIS, although high grading lesions and positive or close surgical margins are two important predictive factors in DCIS recurrences. The adjuvant radiotherapy has decreased the rate of ipsilateral local recurrence about 60%. In this article, we evaluated the recurrence rate as DCIS as well as invasive breast cancer in patients with DCIS undergoing breast conserving surgery (BCS) and intraoperative electron radiotherapy (IOERT).

Methods: Data were derived from Cancer Research Center database from 38 pure DCIS cases who had received intraoperative radiation therapy between 2012–2017. Intraoperative electron radiotherapy (IOERT) was performed according to Iran's intraoperative radiation therapy consensus.

Results: The median age of the patients was 55 years and median histological lesion size was 1.8 centimeters. Number of extracted lymph nodes had a median of 1 and all extracted nodes were negative. Hormonal therapy was performed in 42.1% of patients. IOERT was done as radical full exposure for 86.9% of cases and as boost dose for 13.1% of cases, who needed to complete radiotherapy by external beam. One case in the group received boost dose and 4 cases in the group received full dose had recurrence. The median follow-up of patients was 31 months. Pathology of recurrence was reported as DCIS in 3 cases and invasive breast cancer in 2 of them.

Conclusion: There is not a lot of data on the effectiveness of IOERT in DCIS management. Although there are not large number of cases in our study, the local recurrence (13.1%) was only event in our study with 31 months median follow up with no contralateral metastasis, distant metastasis, or death.

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Introduction

Ductal Carcinoma In Situ (DCIS), which has recently been renamed to Ductal Intraepithelial Neoplasia (DIN), refers to proliferating malignant cells within their normal site in ductal and lobular sections with no invasion through he basement membrane with an higher risk for subsequent

development of invasive ductal carcinoma.[1, 2] In this study, we use the term DCIS instead of DIN.

Consideration of DCIS as a specific disease, gradually happened in the first half of the twentieth century.[3,4] Due to a lack of invasion through the basement membrane in DCIS, it is classified as a nonlethal type of cancer and a precursor to invasive breast cancer.

Previously, DCIS consisted of only about 1-2% of newly diagnosed breast cancers.[3] But considering the aging of the population, increases in screening and diagnostic mammography[5], DCIS consists 20-30% of newer cases of breast cancer in some Western countries nowadays.[6]

The main goal of DCIS treatment is prevention of local recurrence[6], and choosing the method with minimum side effects due to the noninvasive nature of it.[7]

Relative Risk (RR) of invasive ductal carcinoma for intraductal hyperplasia without atypia is 1.5-2%, and with atypia is 4-5%. The RR of invasive ductal carcinoma for DCIS is 8-10%[8], but the main problem is the lack of distinction between the three grades of DCIS (low, intermediate and high) with regards to the relative risk.

According to a contemporary cohort study conducted by the Mayo Clinic, the 12 year follow-up RR for Atypical Ductal Hyperplasia (ADH) in developing breast cancer is about 20.4% and after 25 years this RR increases up to 29%.[9]

Previously, mastectomy was the standard choice for DCIS in all patients.[3] Nowadays it has changed from radical mastectomy to other procedures that are less disfiguring, such as lumpectomy, followed by post-operative radiation and adjuvant hormonal therapy.[4, 10] Since DCIS is a heterogeneous lesion, a single therapeutic protocol is not quite effective for this lesion 4, and management protocols are determined based on the physician's judgement. Much of the controversy in management of DCIS is related to the fact that the survival rate of DCIS is about one hundred percent and there is no data yet demonstrating how the current treatment for DCIS directly affects its survival.[11, 12] Annual risk of local recurrence in DCIS patients who only undergo breast conserving surgery is about 1-2%.[12]

The risk of axillary metastasis in DCIS is less than 4%, thus, axillary lymph node dissection is not necessary to be done.[4,6] Although cytotoxic chemotherapy is not indicated in the treatment of DCIS[4,6], patients may benefit from hormonal therapy. Five years of hormonal therapy in patients with positive estrogen receptor results in a 30% reduction in the relative risk of local recurrence.

The natural history of DCIS is related to its pathologic grade.[13] High grade lesions and positive or close surgical margins are two important predictive factors in DCIS recurrences.[6]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B06 showed a 43% recurrence rate in patients treated with local excision alone, half of which were invasive recurrences. The addition of radiation and careful cytological review of margins significantly improved the local control.[4] In the NSABP B17 trial, the adjuvant radiation therapy decreased the rate of ipsilateral local recurrence about 60%.[4, 6, 14] Although the benefit of post-operative radiotherapy is shown, some of the patients did not receive adjuvant radiotherapy due to their lack of compliance, aging, the distance between radiotherapy center and duration of the radiotherapy course.[15]

Accelerated partial breast irradiation (APBI) is an alternative method for whole breast irradiation, which limits the exposure only to normal breast tissue areas. Intraoperative radiation therapy is a method of Accelerated Partial Breast Irradiation (APBI) where the whole dose of radiation is delivered to the identified tissue at the time of surgery and before the wound site is closed.[15] It seems that this method of radiation therapy increases the patient's compliance and satisfaction.

According to the TARGIT-A study, intra-operative radiation therapy (IORT) is a great choice for certain women with early stage breast cancer.[16]

Many patients who were unable to complete the six week course of radiotherapy, chose radical mastectomy[17], even if the exposure access is easy. If it is shown that one session of intraoperative radiotherapy is equally as effective as standard radiotherapy, this problem would be resolved. IORT may be effective for selective patients after BCS.[18,19] There is limited data on the efficacy of IORT in the management of DCIS.[17,18] In this study, we evaluated the recurrence rate as DCIS or invasive breast cancer in patients with DCIS who had undergone BCS and IORT.

Methods

This study was done between 2012 and 2017 at the Cancer Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran. A total of 38 patients with pure DCIS and with DCIS and Paget's disease of breast were treated with breast conserving surgery and IORT at Khatam-Ol-Anbia Hospital, Tehran, Iran. Patient factors recorded included age, age at diagnosis, tumor size, tumor histologic grade, marital status, family history, tumor differentiation, sentinel and axillary lymph node status, surgical margins, estrogen and progesterone receptor status and whether hormonal therapy was received by patients or not.

According to the IRAN IORT consensus IRIOeRT (the society of Islamic Republic of Iran IOeRT) criteria (table 1), patients received either the radical dose (21 Gy) radiotherapy or the boost dose (12 Gy) to the tumor bed during surgery. Four patients, who

Table 1.IRIORT consensus for radical IOeRT

Factors	Suitable	Possible	Contraindicated
Age (year)	≥ 45	44 - 40	< 40
Tumor size (cm)	< 3	3 -3.5	> 3.5
Margin	Negative	Negative	Positive
Grade	1 and 2	Any	-
Lymphovascular invasion	Negative	Any	-
ER, PR	Positive	Any	-
Multicentricity	No	No	Yes
Multifocality	No	Yes	-
IDC	Yes	Yes	-
ILC	Yes	Yes	-
Pure DCIS, cm	≤ 3	3 - 4	> 4
EIC	< 25	≥ 25	Diffuse
HER2	Any	-	-
LCIS associated	Any	Any	Any
Nodal status	Negative	Negative	Positive
Axillary surgery	SLNB	SLNB or ALND	-
Neoadjuvant chemotherapy	Not Allowed	Not Allowed	If used

were candidates for boost radiotherapy, had received radical radiotherapy due to their problems with access to and distance from the radiotherapy center. One of our patients was under 40 years old who had requested IRIOeRT for her treatment. The initial goal of the study was the assessment of ipsilateral breast DCIS or cancer recurrence status. Assessing the overall survival rate of patients was the secondary goal.

Results

Breast conserving surgery was performed on all of the 38 patients. Patients' age had a median of 55 years (range 33- 76) and the histological size had a median of 1.8 cm (range 0.3 - 5). It is notable that in 8 cases, the exact size of the mass could not be determined by the pathologist. Family history was positive in 23% of cases, and 11.11% in a first-degree family member.

Tumor-free surgical margins were confirmed by pathology in 97.3% of cases, except in one patient in whom deep margins were involved. Lymph nodes extracted as sentinel lymph node were negative in patients who underwent this surgery.

The median number of lymph nodes extracted per patient was 1 (range 0 - 12). High grade DCIS was reported in 65.7% cases, with 47.3% necrosis. Estrogen Receptor (ER) and Progesterone

Receptor (PR) were positive in 68.4% and 50% respectively. Ki-67 as proliferative index was about 20% or more in 42.1% and in 28.9% of cases, was unknown. The lesion types are described in table 2.

Hormonal therapy was prescribed in 42.1% of patients. Tamoxifen and letrozole were used in 66.6% and 33.3% of the patients respectively and none of the patients received chemotherapy.

IORT as boost dose was delivered to 5 patients (13.6%) and one (20%) of them had recurrence later on. The patient with recurrence had extensive retro areolar micro calcification. Radiotherapy dosed at of 16 Gy was delivered to the nipple-areole complex. Furthermore, IORT as radical dose was delivered to 31 (81.5%) patients, with a recurrence rate of 12.9% (4 cases). Overall, local recurrence was documented in 5 cases (13.1 % of patients) with the mean follow up of 31 months (range 8–56 months) and mean age of 50 years. The pathology of recurrence was reported as DCIS in 3 cases and invasive breast cancer in the remaining two.

Distant metastases and mortality were not observed in the studied patients and all patients were alive.

Mastectomy and immediate reconstruction were performed in 4 of the cases with a recurrence and simple mastectomy was done in the remaining one case.

All five patients with recurrence had tumor-free margins in previous pathology reports (table 3). Average tumor size was 1.9 cm (range 0.7-4 cm). Four patients had high grade lesions and one patient had a low-grade lesion without necrosis. Comedo-necrosis was observed in 3 cases. The case with low grade lesion had close superficial margins. The first pathology report of 3 of the cases were pure DCIS, one with DCIS and LCIS and the other, DCIS with Paget's disease. All extracted lymph nodes were negative. Four cases with recurrence received full radiotherapy and one patient received boost IORT plus external radiotherapy. Four patients had positive ER/PR receptor status. Ki-67 marker in 2 of the 5 patients with recurrence was over 20%. Moreover, two patients had positive family history and 4 of them had received hormonal therapy. Table 3 demonstrated the characteristics of the patient and tumor.

Table 2. Patients and tumor charcteristics

Variabels		No
Age	< 40	1
	≥ 40	37
Pathology	DCIS	28
	Paget's disease	1
	DCIS+ Paget's disease	6
	DCIS+ LCIS	3
Family history	Yes	9
	No	26
IORT type	Radical	33
	Boost	5
Local recurrence	Yes	5
	No	33
Tumor size (cm)	< 2	16
	2-5	14
Tumor grade	Unknown	8
	High	25
	Intermediate	3
	Low	9
Ki-67	<20%	11
	≥ 20%	16
ER	Positive	26
	Negative	11
PR	Positive	19
	Negative	18
Free tumor margins	Yes	37
	No	1

Discussion

DCIS is a heterogeneous disease. The treatment strategy is controversial due to its excellent prognosis.[3] The main purpose of treatment is to choose a management plan which reduces local recurrence and does not create unnecessary morbidity.

Breast conserving surgery with or without adjuvant radiotherapy are the treatments of choice for DCIS; however, it depends on the size of lesion, grading and margin status. The recurrence rate in ipsilateral breast decreased by 50% in DCIS patients when administering radiotherapy after breast-conserving surgery.[14]

According to literature, most local recurrences of DCIS are in the lumpectomy cavity. It seems that intraoperative radiation to tumor bed proves to be sufficient for selected cases and local treatment can be completed in one session to increase the patient's compliance.

Although the women who had received intraoperative radiation therapy had higher rates of local recurrence, data on the effectiveness of IORT in DCIS patients is not adequate.

In a study conducted by Solin et al., it was shown that the 12-year rate of developing an ipsilateral breast event for DCIS cases who had been treated with excision without radiation was 14.4% and for patients with low- or intermediate-grade lesions, 2.5 cm or less in size and 24.6% for patients with high-grade DCIS, 1 cm or less in size. The 12-year rate of developing invasive breast cancer for DCIS cases created with excision without radiation was 7.5% and 13.4%, respectively for the low or intermediate grade lesions, 2.5 cm or less in size and high grade lesions, 1 cm or less in size.

A study conducted by Donker et al. evaluated recurrence rate and outcomes during a 15-years follow up in DCIS patients who had undergone breast conserving surgery with or without radiotherapy, from the EORTC 10853 Randomized Phase III trial. This study showed that development of a local recurrence was seen in almost one in three non-irradiated women after local excision for DCIS. Radiotherapy nearly halved the risk of local recurrence.

Polgár et al. reviewed a retrospective series of 10,194 patients. The 10-year rate of local recurrence with and without radiotherapy were 9 - 28% and 22-54% respectively. In four large randomized controlled trials (NSABP-B-17, EORTC-10853, UKCCCR, Swe DCIS; 4,568 patients,), 50 Gy whole-breast radiotherapy significantly decreased the 5-year local recurrence rate from 16 - 22% to 7 - 10% respectively. In a recent meta analysis of randomized trials, Polgár concluded that addition of radiotherapy to breast conserving surgery reduces the risk of both invasive and in situ recurrences by 60%.[22]

Table 3. Characteristics of patients with tumor recurrence

variable	Free Surgical Margin	Age	First Pathology	ER and PR	Ki67	Family history	Tumor size	Grade	Lymph node	Radiation type	Recurrence	Surgery
Patient 1	Yes	33	DSIC+Paget's	Positive	15%	No	4 cm	High	Negative	Radial	Invasive	SSM*
Patient 2	Yes	50	DCIS	Positive	20-25%	Yes	3 cm	High	Negative	Radial	Invasive	SSM
Patient 3	Yes	47	DSIC+LCIS	Negative	10%	No	1 cm	Low	Negative	Boost	DCIS	SSM
Patient 4	Yes	64	DCIS	Positive	30%	Yes	1 cm	High	Negative	Radial	DCIS	SSM
Patient 5	Yes	56	DCIS	Positive	15%	No	0.7 cm	High	Negative	Radial	DCIS	Mastectomy

** SSM: Skin sparing mastectomy*

A meta analysis by Viani et al. on a total of 3665 patients with DCIS, reduced significantly in recurrence of invasive and DCIS ipsilateral breast cancer with an odds ratio of 0.40 without any differences in distant metastases. Viani reported more contralateral breast cancer after adjuvant radiotherapy, 3.85%, versus observation, 2.5%. The probability of contralateral breast cancer was 1.53 times higher (95% CI 1.05 – 2.24, P = 0.03) in the radiotherapy arms of the study.[23]

In the study conducted by Bijker et al., the local recurrence after 10 years was evaluated as follows: 74% of patients with DCIS who were treated with local excision and 85% of patients who were treated by local excision and radiotherapy were recurrence free in the 10-year period (log-rank P<0.0001; hazard ratio = 0.53). Based on their research, DCIS and invasive local recurrence reduction rate werereported at 48% and 42%, respectively. The rate of death and distant metastasis was low in both groups.

Rivera et al. reported that 91.4% of patients with DCIS were successfully treated with BCS and IORT alone, only 2 cases from 35 patients suffered local recurrence of cancer after DCIS, with median follow-up of 42 months (range of 2 - 83 months). The primary pathology of one of the cases was high grade DCIS and the other was intermediate grade DCIS, resulting in a 5.7% local recurrence rate in patients with DCIS who had undergone BCS and IORTwithout any deaths or distant recurrences.

In a study by Rashtian et al., DCIS patients were treated with BCS and IORT. The median follow-up was 18.3 months and only one patient suffered local recurrence, the primary histology was high grade DCIS. The 3-year actuarial local control rate was 93.3%.[19]

In our study, 38 patients with mean follow-up of 31 months (range 8–56 months) were reported. Local recurrence occurred in 5 cases. The overall survival rate was 100%. Disease free survival rate was 86.8%. No death or distant metastases were observed. A summary of research studies containing outcomes of IORT in patients with DCIS is available in table 4.

Table 4. Summary of similar studies (similar inclusion criteria)

Author`s name	Number of cases	Follow-up length (Months)	Local recurrence	Primary histologic grading (cases with recurrence)	Systemic recurrence
Current study	38	38	38	High 4/ low 1	0
Rivera et al.[17]	35	35	35	High 1/ intermediate 1	0
Rashtian et al.[19]	23	23	23	High 1	0

In conclusion, There is not enough data on the effectiveness of IORT in DCIS management. Although there is not a large number of cases in our study, the finding of this study showed 13.1 percent local recurrence in a median follow up of 31 months. There was no involvement in the contralateral breast, distant metastasis or death in the study population., distant metastasis, or death. Further studies with more cases and longer follow up periods are needed for better evaluation of the effectiveness of IORT in management of DCIS.

Conflict of Interest

This study did not use any financial support from the pharmaceutical or medical instruments companies in any steps of design, implication, and report.

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